quired. The new Commissioner, who inherited this headache, may insist that henceforth scientific considerations shall not be overridden by profits and politics.

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Severe Hypophosphatemia

A Previously Ignored Cause of Cellular Dysfunction

TWO RECENT, coincidental advances in hospital-based diagnostic and therapeutic techniques have focused attention on serum phosphorus levels. The development of the "twelve channel" apparatus in which several blood chemistries are obtained in semiautomated fashion has placed serum phosphorus in the routine category of blood chemistry determinations. The resulting increase in serum phosphorus data has quickly led to the perception that hypophosphatemia is not vanishingly rare, and in fact, may occur in more than 30 different clinical situations—as noted in the exhaustive review of the subject by Dr. Fitzgerald elsewhere in this issue. During this same period "intravenous hyperalimentation," the infusion of hypertonic solutions of amino acids and glucose, has become an increasingly popular therapy for the repletion of cachectic patients. In such patients extraordinary decrements in serum phosphorus (frequently below 0.5 mg per 100 ml) are commonplace in many surgical and pediatric units.

In our own institution, the University of Minnesota Hospitals, as many as eight patients receive such therapy at any time. From this experience we have described a potentially fatal syndrome which occurs in close association with the profound hypophosphatemia manifest by these patients.[1] Thus, shortly following development of hypophosphatemia, the patients suffer paresthesias, muscular weakness and lethargy, which may progress to convulsions and coma. At this time anemia regularly occurs, and its sudden onset and accompanying reticulocytosis suggest that its cause involves hemolysis. In many of the patients, mucosal bleeding develops, such as epistaxis and mild gastrointestinal hemorrhage; finally, severe infection—both bacterial and fungal—may occur in as many as two thirds of these patients.[2] As reviewed by Fitzgerald, evidence has been gathered that the anemia, hemostatic defects and infection propensity reflect adenosine triphosphate (ATP) deficiency in red cells, platelets and granulocytes, respectively—a deficiency caused, in turn, by the lessened availability of phosphate substrate for ATP synthesis by the blood cells.[3,4] Identical defects have been produced in starved, hyperalimented dogs in which, as in patients, complete reversibility of these abnormalities occurs when phosphate is supplemented.[5] The nature of the neurologic defects in hyperalimentation, although originally thought to reflect similar ATP deficiency in nerve cells, may be more complex. Certainly phosphate supplementation is not as dramatically efficacious in treating this part of the syndrome, and attempts to document brain ATP deficiency have to date not been successful.

It is possible that the neurologic symptoms and rapid muscular fatigability manifest in a hypophosphatemic patient may reflect a deficiency in another phosphorylated compound of red blood cells, 2,3 diphosphoglyceric acid (2,3 DPG). This organic phosphate compound, like ATP, is also critically dependent upon the availability of serum phosphate for its synthesis. Moreover, 2,3 DPG seems to be a crucial regulator of oxygen delivery to tissues; thus it binds to the hemoglobin molecule, thereby diminishing its affinity for oxygen.[6] Enhanced oxygen delivery to tissues results; conversely, oxygenation is predictably inefficient if red cells are deficient in 2,3 DPG. That cerebral hypoxia may occur during hypophosphatemia on this basis is suggested by observations in a profoundly hypophosphatemic, alcoholic patient who was infused with large quantities of sodium bicarbonate.[7] The patient rapidly became confused,

lapsed into coma and ceased spontaneous respirations, requiring mechanical support for the following 48 hours. Since alkalosis shifts the hemoglobin-oxygen saturation curve in the same direction as does 2,3 DPG deficiency (that is, to the "left"), the effects of bicarbonate and hypophosphatemia (and therefore 2,3 DPG deficiency) were additively, and crucially, deleterious to this patient.

Analogous considerations have suggested to Dr. Carroll Leevy that some confusional states noted in malnourished alcoholic patients may also reflect red cell 2,3 DPG deficiency with resulting cerebral hypoxia. Administration of phosphate to some such patients has improved their sensorium, while concomitantly increasing red cell 2,3 DPG and decreasing spinal fluid pyruvate and lactate levels (discussion in reference 1).

These observations indicate clearly that administration of alkali to hypophosphatemic persons may be particularly hazardous. Patients with diabetic, or uremic, acidosis are potential victims of such well-intentioned maneuvers. Thus, the acidotic diabetic patient upon entry to hospital frequently manifests diminished red cell 2,3 DPG levels. This deficiency results mainly from the inhibitory effect of acidosis on red cell glycolysis (and hence 2,3 DPG synthesis). The deficiency worsens if hypophosphatemia supervenes, as it often does, during insulin therapy. Fortunately, the predicted inefficient release of oxygen by hemoglobin in this situation is ameliorated by the opposing beneficial effect on oxygen unloading of acidosis itself (the Bohr effect). Rapid correction of acidosis by administration of alkali reverses this ameliorating effect which may partially account for the not-infrequent disasters encountered with bicarbonate therapy. Similarly, uremic patients are frequently treated with antacid chelators to reduce serum phosphate levels and thereby inhibit secondary hyperparathyroidism stimulated by hyperphosphatemia. Such therapy is frequently overly-vigorous so that patients actually become hypophosphatemic. Rapid correction of acidosis, especially by hemodialysis in these patients, may lead to tissue hypoxia—a sequence which probably, at least partially, explains the postdialysis syndrome of lethargy and weakness noted in many such patients.

It should be evident from the above and from Dr. Fitzgerald's excellent review, that serum phosphorus homeostasis is a critical area for future investigation. For the present, rigorous maintenance of serum phosphorus should prevent many of the previously-unperceived, deleterious consequences associated with its deficiency.

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Federal Support for Assumptions or for Science?

IN HIS PRESIDENTIAL ADDRESS to the Western Society for Clinical Investigation (which appears elsewhere in this issue), Dean Mason calls attention to a matter which should be of enormous concern to both the medical profession and the public. This is the substantial shift of dollar support away from basic research in medical science, which leads to new discoveries and fundamental progress, to programs which are expected to fill some presumed or assumed need for specific research to solve some specific unknown which will have significant impact in patient care. Further, substantial federal dollar support has been diverted entirely from support of medical research and is being used to impose costly yet untested assumptions on the health care delivery system. For example, there has been very little real testing of the assumptions inherent in Health Maintenance Organizations (HMO's), Professional Standards Review Organizations (PSRO's), the Health Services Agencies (HSA's) or of the approach of the Federal Drug Administration (FDA).